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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,826	02/24/2002	Alan P. Wolffe	8325-0014.20	4340

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

1/26/05 RS

Office Action Summary	Application No.	Applicant(s)	
	10/084,826	WOLFFE ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-14,19-36 and 40-73* is/are pending in the application.

4a) Of the above claim(s) *1-7,10-14,19-33 and 44-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/08/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

It is noted that Applicants are attempting to request for a corrected filing date for the instant application. The appropriate request should be made by petition to the Office of Petitions. (see, 37 CFR 1.10 (c); MPEP 506.02).

Election/Restrictions

Applicant's election without traverse of group IV in the reply, filed on 10/18/2004, is acknowledged. As such claims 1-7, 10-14, 19-33 and 44-73 are withdrawn from consideration as drawn to non-elected subject matter. Claims 34-36 and 40-43 are under consideration in this action.

Claim Objections

Claim 34 is objected to because of the following informalities: the claim is improperly dependent from a successively numbered claim. However, as the claims' metes and bounds are clear notwithstanding the improper numbering, the claim has been examined on the merits. Prior to issuance the claims will be renumbered. (MPEP 608.01(n)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 34-36 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the claims are directed to a genus of fusion molecules having structures with a requisite functionality, i.e., DNA binding and enzymatic functionality. Therefore, the genus comprises two distinct structures where each structure is defined by a particular function (i.e. DNA binding domain (DBD) and enzymatic domain) as well as undefined functional fragments of the enzymatic component or of the remodeling complex. In addition, claim 40 encompasses non-protein fusion molecules where the DNA binding domain of the fusion molecule can be a chemical compound (e.g., interchelating agen), nucleic acids or proteins. As such, with respect to claim 40 the genus of fusion molecules is broadened even further.

Therefore claims encompass a large number of fusion structures that must have the requisite function of binding DNA and facilitating chromatin remodeling or performing the recited enzymatic functions (i.e. histone-methylase/demethylase, -kinase/phosphatase, -ubuiquitinase, -ADP ribosylase or -protease) in any cell/organism. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification discloses a fusion polypeptide comprising a DBD that recognizes target sequences in the human VEGF gene, which is alternatively fused to BAF155, MBD1, MBD2, MBD3, DNMT and KRAB. (e.g., Figs. 6-7; Examples 2-13). However, none of the foregoing defined structures functions as a histone-methylase/demethylase, -kinase/phosphatase, -ubuiquitinase, -ADP ribosylase or –protease. In addition, with regard to the disclosed structures no further clarification of potential functional fragments is provided, where for example, a single amino acid change could abrogate chromatin-remodeling functionality. As the specification points out, chromatin remodeling can occur through DNA or histone covalent modification. The disclosed embodiments are directed exclusively to DNA modification, while the claims encompass a genus that includes both DNA or histone covalent modification. There are no embodiments disclosed of structures or functional fragment of structures that function to covalently modify histones.

The specification provides guidance on assaying for chromatin remodeling, however such guidance could provide sufficient support for an enablement requirement, but are not sufficient support for the written description requirement. Moreover, "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117). Furthermore, knowing that a product may exist, in the absence of what that product consists of (i.e. actual structure) is not a description of that product. (*University of California v. Eli Lily and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). In sum, the specification fails to describe the structure of any enzymatic components that operate as a histone-methylase/demethylase, -kinase/

phosphatase, -ubuiquitinase, -ADP ribosylase or -protease. In addition the specification does not describe the structure of any functional fragments of either the preceding histone modifiers or the disclosed structures (supra, Figs. 6-7; Examples 2-13). The specification does not provide any structures comprising non-protein fusion molecules (e.g., genus of molecules encompassed by claim 40).

Furthermore, knowledge in the art does supplement the instant disclosure's omission of a sufficient description. For example, "In contrast to the relative wealth of information about the large number of acetyltransferases and deacetylases, relatively little is known about the enzymes that generate other histone modifications". (Grant, P. Genome Biology. 2001; 2(4):1-6, p. 3, col. 2, ¶ 2). In addition, a vast number of other histone modifications await discovery or further investigation, which include ADP-ribosylation and ubiquitanation. (Id., p. 4, col. 2, last ¶). For example, a particular protein factor may be recognized as having a histone modifying activity, but the actual structure (i.e. enzymatic domain) for said activity would not necessarily be identified. (e.g., Pham et al. Science. 2000; 289:2357-60; showing histone ubiquitin activity for $TAF_{II}250$). In essence, the evidence in the art may recognize that certain histone covalent modifiers are out there, but the defined structure of such modifiers or functional fragments thereof is not known.

Given the enormous breadth of the fusion molecules, comprising DNA binding domains and enzymatic components or chromatin remodeling complexes, including functional fragments thereof, encompassed by the rejected claims, including non-protein-protein fusion molecules, and given the limited description in the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to

described the broadly claimed genus. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. **Claims 34-35 and 40-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Cox, III et al. (US 6,534,261; hereinafter the '261 patent).**

The claims are directed to a fusion molecule having a zinc-finger DNA binding domain and an enzymatic component of a chromatin-remodeling complex or functional fragment thereof having histone methylase activity. The limitation for an enzymatic component is interpreted as broadly as reasonable to be directed to any protein domain being directly or indirectly involved in histone methylation.

The '261 patent teaches a fusion molecule having a zinc finger binding DNA binding domain (e.g., Fig. 5; depicting ZFP-KRAB fusion protein; columns 51-52), thus teaching a polypeptide and the polynucleotide encoding said polypeptide. The chimeric fusion molecule is introduced into cells. (e.g., Figs. 8-9). The KRAB domain interacts indirectly with HP1 through KAP-1 and an intrinsic property of HP1 is involvement in histone methylation. (e.g. Ayyanathan et al. 2003. Genes & Dev. 17:1855-1869; see whole document; especially p. 1866, col. 1, ¶¶ 2-3, bridging to col. 3, ¶¶ 1-3; this post filing art is merely cited to show the intrinsic property for the KRAB enzymatic component as being a member of a chromatin remodeling complex). Therefore, the '261 patent anticipate the rejected claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. **Claims 34-35 and 40-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 34-37 and 40-42 of copending Application No. 09/844,508 in view of Cox, III et al. (US 6,534,261; hereinafter the '261 patent) as evidenced by Ayyanathan et al.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are related to the reference claims as species and genus type claims. For example, reference claims 34 is directed to a fusion polypeptide having a DNA binding domain and a component of a chromatin remodeling complex and reference claim 37 further limits the component as an enzymatic component. Similarly, instant claim 40 is directed to a fusion molecule having a DNA binding domain and an enzymatic component, but where the enzymatic component is selected from a group of histone modifiers (e.g., methylase, kinase, phosphatase, ubiquitinase). Other than the base claims, both the reference and instant claims are directed to indistinguishable subject matter (e.g., (reference claim:instant claim); polynucleotide (40:41), polypeptide (34:35) and cells (41-42:42-43) comprising the fusion molecule).

In addition, the reference claims are specifically directed to components of a chromatin remodeling complex that covalently modify histone (e.g., reference claim 39). The reference claims are not specifically directed to an additional enzymatic component of a chromatin remodeling complex wherein the complex is involved in histone modification such as histone methylation (e.g., instant claim 40).

However, the '261 patent teaches a fusion molecule having a zinc-finger DNA binding domain module and an enzymatic component of a chromatin remodeling complex (e.g., KRAB domain; columns 51-56;Fig. 5).

KRAB domain is a component of a chromatin remodeling complex that intrinsically has the property of histone methylation. (supra, Ayyanathan et al. 2003. p. 1866, col. 1, ¶¶ 2-3, bridging to col. 3, ¶¶ 1-3). Furthermore, as in the reference claim 1, the '261 patent teaches that the fusion molecule is used to modify chromatin structure in a particular region of interest, for the benefit of obtaining gene regulation. (Id.)

Therefore, it would have been obvious to include additional components of a chromatin remodeling complex that covalently modify histones, such as methylation. One would have been motivated to include additional embodiments of chromatin remodeling complex components having histone methylation activity, so as to obtain the benefit of broader coverage of factors that can be utilized to regulate gene expression (e.g., in cells examined in culture). Given that reference claims are drawn to fusion molecules that encompass the instant claims, and given that the '261 patent teaches enzymatic components that can be used in fusion molecules to modify chromatin in a manner as claimed in instant claim 40, there would have been a reasonable expectation of success to claim additional species within the genus claimed in the reference application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER